An international consensus statement on the management of postoperative anaemia after major surgical procedures

Muñoz, M ; Acheson, A G ; Bisbe, E ; Butcher, A ; Gómez-Ramírez, S ; Khalafallah, A A ; Kehlet, H ; Kietaibl, S ; Liumbruno, G M ; Meybohm, P ; Rao Baikady, R ; Shander, A ; So-Osman, C ; Spahn, D R ; Klein, A A

Abstract: Despite numerous guidelines on the management of anaemia in surgical patients, there is no pragmatic guidance for the diagnosis and management of anaemia and iron deficiency in the postoperative period. A number of experienced researchers and clinicians took part in a two-day expert workshop and developed the following consensus statement. After presentation of our own research data and local policies and procedures, appropriate relevant literature was reviewed and discussed. We developed a series of best-practice and evidence-based statements to advise on patient care with respect to anaemia and iron deficiency in the postoperative period. These statements include: a diagnostic approach to iron deficiency and anaemia in surgical patients; identification of patients appropriate for treatment; and advice on practical management and follow-up that is easy to implement. Available data allow the fulfilment of the requirements of Pillar 1 of Patient Blood Management. We urge national and international research funding bodies to take note of these recommendations, particularly in terms of funding large-scale prospective, randomised clinical trials that can most effectively address the important clinical questions and this clearly unmet medical need.

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Review

An International Consensus Statement on the management of postoperative anaemia after major surgical procedures

M. Muñoz,[1] A. G. Acheson, [2] E. Bisbe,[3] A. Butcher,[4] S. Gómez-Ramírez,[5] A. A. Khalafallah,[6] H. Kehlet,[7] S. Kietaibl,[8] G. M. Liumbruno,[9] P. Meybohm,[10] R. Rao Baikady,[11] A. Shander,[12] C. So-Osman,[13] D. R. Spahn,[14] and A. A. Klein[15]

1 *Professor, Department of Surgical Specialties, Biochemistry and Immunology, School of Medicine, University of Málaga, Málaga, Spain*
2 *Associate Professor, Department of Colorectal Surgery, Nottingham Digestive Diseases Centre, National Institute for Health Research Biomedical Research Unit, Nottingham University Hospitals, Nottingham, UK*
3 *Consultant, Department of Anaesthesia, University Hospital Mar-Esperanza, Barcelona, Spain*
4 *Research Fellow, Division of Surgery, University College London, London, UK*
5 *Consultant, Department of Internal Medicine, University Hospital Virgen de la Victoria, Málaga, Spain*
6 *Professor, Department of Haematology and Medicine, Launceston General Hospital, Launceston, and Menzies Institute for Medical Research, University of Tasmania, TAS, Australia*
7 *Professor, Section of Surgical Pathophysiology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark*
8 *Professor, Department of Anaesthesia and Intensive Care, Evangelical Hospital, Vienna, Austria*
9 *General Director, Italian National Blood Centre, National Institute of Health, Rome, Italy*
10 *Professor, Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt, Germany*
11 *Consultant, Department of Anaesthesia, The Royal Marsden NHS Foundation Trust, London, UK*
12 *Professor, Anaesthesiology, Critical Care and Hyperbaric Medicine, Englewood Hospital and Medical Centre and Director, TeamHealth Research Institute, Englewood, New Jersey, USA*
13 *Consultant, Department of Transfusion Medicine, Sanquin Blood Bank, Amsterdam and Department of Internal Medicine, Groene Hart Hospital, Gouda, The Netherlands*
14 *Professor and Chairman, Institute of Anaesthesiology, and Head of Anaesthesiology, Intensive Care Medicine and Operating Room Management, University Hospital of Zurich, Zurich, Switzerland*
15 *Consultant, Department of Anaesthesia and Intensive care, Papworth Hospital, Cambridge, UK*

Correspondence:
Prof. Manuel Muñoz
Department of Surgical Specialties, Biochemistry and Immunology
School of Medicine, University of Málaga
29071-Málaga (Spain)
E-mail: mmunoz@uma.es

Content

Summary

Despite numerous guidelines on the management of anaemia in surgical patients, there is no pragmatic guidance for the diagnosis and management of anaemia and iron deficiency in the postoperative period. A number of experienced researchers and clinicians took part in a two-day expert workshop and developed the following consensus statement. After presentation of our own research data and local policies and procedures, appropriate relevant literature was reviewed and discussed. We developed a series of best-practice and evidence-based statements to advice on patient care with respect to anaemia and iron deficiency in the postoperative period. These statements include: a diagnostic approach for iron deficiency and anaemia in surgical patients; identification of patients appropriate for treatment; and advice on practical management and follow-up that is easy to implement. Available data allow the fulfilment of the requirements of Pillar 1 of Patient Blood Management. We urge national and international research funding bodies to take note of these recommendations, particularly in terms of funding large-scale prospective, randomised clinical trials that can most effectively address the important clinical questions and this clear unmet medical need.

Recommendations for best clinical practice

- All patients who have undergone major surgery (defined as blood loss > 500 ml or lasting > 2 hrs) and who had pre-operative anaemia or moderate-to-severe blood loss during surgery must be screened for anaemia after surgery.
- During recovery from uncomplicated major surgery, haemoglobin concentrations should be monitored, either by standard laboratory or point-of-care testing, on a regular daily basis, at least until the third postoperative day, to detect anaemia (haemoglobin < 130 $g.l^{-1}$ for men, <120 $g.l^{-1}$ for women).
- Postoperatively, iron deficiency should be defined by ferritin concentration <100 $\mu g.l^{-1}$, ferritin <100-300 $\mu g.l^{-1}$ and transferrin saturation <20%, or reticulocyte haemoglobin content <28 pg. High blood loss during surgery may also indicate the need for iron replacement in anaemic patients.
- In the postoperative period, when the administration of iron is necessary, early intravenous iron therapy is recommended, after considering contraindications. Where possible, it should be administered using a single high-dose preparation for the repletion of iron stores
- For non-cancer patients with severe postoperative anaemia and inflammation-induced blunted erythropoiesis, or those declining blood transfusion, we suggest considering additional treatment with an erythropoiesis stimulating agent.
- If patient blood management measures did not prevent the development of severe postoperative anaemia, the adoption of a restrictive transfusion threshold is recommended (haemoglobin level: 70-80 $g.l^{-1}$, depending on patient's comorbidities) is recommended in most adult, clinically-stable hospitalised patients.
- We recommend establishing a Patient Blood Management expert group in every hospital.

Why was this consensus statement developed?

The concept 'patient blood management (PBM) is defined as "*the timely application of evidence based medical and surgical concepts designed to manage anaemia, optimise haemostasis, and minimize blood loss in order to improve patient outcomes after surgery*" [1]. Patient blood management has been shown to reduce transfusion, healthcare costs and morbidity and mortality [2]. Treatment of pre-operative anaemia and isolated iron deficiency are crucial measures for PBM [3.4]. However, detection and early treatment of pre-operative anaemia and iron deficiency is an accepted logistical challenge and, as a consequence, some patients may undergo surgery without the chance to address their anaemia [3]. In addition, there has been increased emphasis on the use of restrictive transfusion thresholds in order to accelerate recovery and discharge after surgery as well as improve outcomes and reduce transfusion requirements, which may have led to overlooking potential opportunities to optimise anaemic patients and improve their functional recovery [5,6]. Therefore, an additional focus on the early detection and treatment of postoperative iron deficiency and anaemia is a novel and complementary measure within the concept of PBM which allows the attending physician to target patients who lost significant red cell mass during surgery and may require specific attention postoperatively or post-discharge [7].

How does this consensus statement differ from other available statements and/or guidelines?

There are a number of statements and guidelines from professional associations recommending a systematic approach to this problem for the management of preoperative anaemia [1,7-15]. Most of these guidelines also recommend the use of a restrictive transfusion threshold for treating acute postoperative anaemia, but recommendations for pharmacological management of anaemia are scarce or even absent [1,7-15]. The aim of this document is to update and utilise the few current recommendations therein and with a panel of experts provide a working practice document, based on scientific evidence and clinical experience, on 'how to' feasibly introduce these postoperative anaemia guidelines into clinical practice. Therefore, our goal is to provide pragmatic, clear easy-to-follow clinical guidance for the diagnosis

and treatment of postoperative anaemia and iron deficiency in order to improve patient recovery, reduce the need for blood transfusion and improve functional outcomes in a cost-effective manner. Our recommendations are intended for non-actively bleeding adult patients in whom all the principles of PBM have been implemented pre- and intra-operatively for the prevention of postoperative iron deficiency and anaemia.

Definition, prevalence and pathophysiology of postoperative anaemia

Postoperative anaemia may be present in up to 80-90% of patients undergoing major surgery, although this prevalence varies widely according to different definitions [16,17]. Anaemia is defined by the World Health Organization (WHO) as a haemoglobin concentration <130 $g.l^{-1}$ for men, <120 $g.l^{-1}$ for non-pregnant women and <110 $g.l^{-1}$ for pregnant women [18]. Although debated [19], and since these definitions are widely accepted, they may apply to postoperative patients. However, we previously pointed out that the WHO criteria for the definition of anaemia may not be reliable for the classification of non-pregnant women undergoing surgical procedures with expected moderate-to-high blood loss. Women have lower circulating blood volumes and reduced red cell mass compared to males, but the same procedures performed in either *gender* often result in comparable amounts of blood loss, resulting in higher transfusion rates in females [4]. Therefore, pre-operative anaemia in non-pregnant women should be defined as for men as a haemoglobin concentration < 130 $g.l^{-1}$.

According to the WHO, postoperative anaemia could be classified as mild (haemoglobin 100-119/129 $g.l^{-1}$), moderate (haemoglobin 80-100 $g.l^{-1}$) or severe (haemoglobin <80 $g.l^{-1}$) [18].

Although multi-factorial in origin (Table 1), pre-operative anaemia, peri-operative blood loss (surgical bleeding, coagulopathy, phlebotomies, etc.), and postoperative blunted erythropoiesis are the main contributing factors to postoperative anaemia after major surgery. Haemodilution due to excessive fluid administration, which may cause 'dilutional' anaemia or aggravate pre-existing anaemia, and other nutritional

deficiencies (e.g., vitamin B_{12}, folic acid) and pharmacological interactions are also contributing factors [20].

Low pre-operative haemoglobin, female sex and smaller body surface area have been identified as risk factors for the development of postoperative anaemia and increased transfusion needs [21]. Additionally, in the general population, the prevalence of anaemia increases with age and older persons are more likely to undergo major surgery and to present with comorbidities, thus increasing the risk of postoperative anaemia, and reducing its tolerability [22,23].

The end of the surgical procedure does not always signify the end of blood loss. Ongoing postoperative blood loss can continue through drains or into traumatised tissue, or due to repeated phlebotomies during a prolonged postoperative period. As such, peri-operative blood loss may result in acute or late postoperative anaemia, especially in patients with the above mentioned risks factors. To avoid the detrimental effects of acute anaemia, packed red blood cells are usually transfused, as a default measure [20]. However, the use of restrictive transfusion threshold, as emphasised in the third pillar of PBM, also contributes to a higher prevalence of moderate-to-severe anaemia on discharge from hospital (haemoglobin concentration <100 $g.l^{-1}$), unless pro-active measures are implemented [20].

Anaemia in the postoperative period, as well as in critical illness, may be aggravated by reduced erythropoietin production and secretion due to inflammatory mediators; blunted bone marrow response to erythropoietin; and decreased iron availability due to down-regulation of intestinal absorption and impaired mobilisation of iron from body stores (Table 1) [24,25]. Inflammatory cytokines stimulate the secretion of hepcidin, a hormone that targets ferroportin, the only known cellular exporter of iron. This induces the internalisation and degradation of ferroportin, thereby largely inhibiting intestinal iron absorption and greatly reducing iron release from body stores (iron sequestration) [26].

What are the unmet medical needs of postoperative anaemia?

The concerns surrounding postoperative anaemia relate to its potential impact on recovery, rehabilitation, hospital re-admission or re-operation, and patients' wellbeing. Reducing allogeneic blood transfusion improves long-term outcome and survival [27]. However, restrictive transfusion protocols have led to patients being discharged with lower haemoglobin levels than before. With the current paucity of data, it remains unclear whether a lowered discharge haemoglobin level may allow optimal functional recovery and quality of life [28-34]. There has been limited research on the consequences of postoperative anaemia in the recovery phase from surgery, with only a small number of studies after cardiac and hip and knee surgery, which demonstrated the association between postoperative anaemia and adverse outcomes such as prolonged recovery, increased mortality and likelihood of re-admission [31-33]. Postoperative anaemia may also potentially be associated with early postoperative myocardial infarction [34]. Correction of postoperative anaemia, as suggested in this consensus statement, is intended to prevent side effects, but studies are urgently needed to prove this.

Diagnosis of postoperative anaemia

When and how to measure haemoglobin concentration?

Measurement of haemoglobin concentration is a routine procedure in postoperative care. Duration of testing for postoperative anaemia depends on the peri-operative bleeding risk associated with the surgical intervention and patient-dependent factors. In most cases of uncomplicated recovery from surgery, a nadir in haemoglobin concentration can be observed within the first 3-4 days after surgery. In patients with major complications following major surgery, however, prolonged hospitalisation and exposure to low haemoglobin levels increase the duration of monitoring required.

Usually, blood gas analysis, capillary sampling (e.g., HemoCue, HemoCue AB, Ängelholm, Sweden) or near-infrared spectroscopy (e.g., Radical-7, Masimo Corporation, Irvine, CA, USA) are performed as a point-of-care assessment, while the full blood count is tested in the central laboratory. The use of non-invasive continuous

haemoglobin monitoring devices instead of phlebotomy may reduce blood loss, pain and discomfort for the patient, but concerns about precision limit routine clinical use. Although the debate focuses on accuracy of a single check [35], the reliability of non-invasive haemoglobin monitoring devices for dynamic changes over time may permit detection of occult bleeding and response to therapy [36].

What are the confounding factors?

In the setting of postoperative care, a number of confounding factors may impact on accurate haemoglobin measurement. Volume overload and haemodilution after major surgery are potential causes for low haemoglobin levels, despite normal and stable red cell mass. Therefore, the diagnosis of anaemia based on simple haemoglobin concentration may be misleading and is confounded by plasma volume derangements resulting in significant over-diagnosis [37]. Potential volume overload should be taken into account and may improve after diuresis.

Similar conditions may be present in the peri-operative setting where prevention of intravascular volume deficit is a cornerstone of peri-operative management. Here, intravascular volume and fluid therapy is fundamental whenever fasting is indicated for medical reasons, in the event of high-fluid turnover rates during major surgery, or in cases of reduced enteral resorption because of sustained vomiting, severe diarrhoea or gastro-intestinal dysfunction following circulatory shock. The primary aim of fluid therapy (crystalloids and colloidal solutions) is the restoration of plasma and blood volume to ensure appropriate cardiac output and tissue perfusion.

Unfortunately, appropriate assessment of the volume status is complex. The diagnosis or quantification of moderate-to-severe volume deficit and volume responsiveness remains difficult, and may be attempted using laboratory variables (e.g. lactate, base excess), positional manoeuvres (passive lifting of legs), new monitoring devices (measuring pulse variability and stroke volume indexes or other preload variables) or echocardiography. Recent guidelines highlight the importance of avoiding hypervolaemia [7]. During postoperative recovery, redistribution and excretion of

fluids may lead to rapid recovery of haemodilution-induced low haemoglobin concentrations.

When and how to measure postoperative iron deficiency?

Although underlying causes of postoperative anaemia are multifactorial, iron deficiency is often present. While pre-operative iron deficiency can be diagnosed on the basis of low ferritin concentrations [4], diagnosis of postoperative iron deficiency is more difficult as ferritin levels may be elevated as part of the acute phase inflammatory response after surgery [38]. Thus, patients undergoing major surgery with a high risk of developing moderate-to-severe postoperative anaemia should have their haemoglobin and iron status checked on the day of surgery, if it has not been already performed in the pre-operative assessment. This may also apply to patients with ongoing bleeding and anaemia (e.g. colorectal cancer) that have been treated in the pre-operative period. As ferritin levels will be not elevated by inflammation immediately after surgery, a postoperative ferritin concentration <100 $\mu g.l^{-1}$ on day of surgery indicates insufficient iron stores to support erythropoiesis after procedures with significant postoperative haemoglobin drop [8].

Further markers for postoperative iron deficiency are transferrin saturation <20% with ferritin concentrations 100-300 $\mu g.l^{-1}$, or reticulocyte haemoglobin content <28 pg. These values and parameters may signal the need for intervention in anaemic patients [38-40].

When should postoperative anaemia be treated?

There is limited supporting data regarding appropriate timing for management of anaemia after surgery including red cell transfusion. Treatment choice depends on severity and type of anaemia, type of surgery, patient comorbidities and presence of any surgical complications.

Iron supplementation should be considered in patients with iron deficiency or significant a significant reduction in postoperative haemoglobin, starting early in the postoperative recovery phase with no major complications [39,42-46]. It is important

to note that there are no studies identifying the best moment to start postoperative iron supplementation.

For non-cancer patients with severe postoperative anaemia and inflammation-induced blunted erythropoiesis or those declining blood transfusion, additional treatment with an erythropoiesis stimulating agent (e-g., recombinant human erythropoietin [rHuEPO]) may be considered. However, we are aware that for patients without a previous indication this is an off-label use of rHuEPO, and recommendations vary across countries [10,12,15].

Red cell transfusion should be restricted to patients with severe anaemia (haemoglobin <70-80 $g.l^{-1}$) and clinical signs and symptoms [7,10-12,47-49]. Red cell transfusion should be considered in patients with active bleeding and in those severely anaemic once bleeding has been stopped [7,10-12,47-49]. However, more research is required on specific transfusion thresholds in specific high-risk patients.

How should patients be treated postoperatively?

Pharmacological optimisation of postoperative haemoglobin and erythropoiesis should allow correction of iron deficiency and rapid recovery from postoperative anaemia which can lead to improved postoperative outcomes and improved quality of life. It may also result in a reduction of patient's exposure to red cell transfusion and its related risk and complications, thus contributing further to improving surgical outcome and patient safety.

Iron therapy: oral vs. intravenous iron?

The National Institute for Health and Care Excellence in the UK (NICE) recommends offering oral iron after surgery to patients with iron deficiency anaemia [12]. However, in the postoperative period, oral medications may not be tolerated or absorbed and have several limitations including frequent gastro-intestinal side effects and, as a consequence, poor treatment adherence. Additionally, the inflammatory response induced by surgery stimulates hepcidin synthesis and release, which in turn inhibits intestinal iron absorption, making oral iron therapy largely ineffective [10,13,50].

Various randomised placebo controlled trials (RCTs) in orthopaedic and cardiac surgery patients have demonstrated that oral iron therapy was not better than placebo in correcting postoperative anaemia and reducing transfusion requirements [51-57].

On the other hand, NICE recommends considering intravenous (i.v.) iron after surgery for patients who have iron deficiency anaemia and cannot tolerate or absorb oral iron, or are unable to adhere to oral iron treatment, as well as for those who are diagnosed with functional iron deficiency [12]. Thus, patients with uncorrected pre-operative iron deficiency (ferritin <100 $\mu g.l^{-1}$) and/or moderate-to-severe postoperative anaemia (haemoglobin <100 $g.l^{-1}$) may benefit from i.v. iron supplementation, which has proven to be more effective than oral iron in a number of surgical settings (On-line appendix 1) [39,42-45,58-62]. Most recent RCTs have shown a benefit of high-dose postoperative i.v. iron (e.g., 1000 mg) as demonstrated by increased Hb and/or reduction of transfusion requirements, and no i.v. iron-related serious adverse events were reported (On-line appendix 1) [39,42,44,45]. Importantly, in orthopaedic surgical patients with postoperative haemoglobin <100 $g.l^{-1}$ and/or uncorrected preoperative iron deficiency, a great rise in Hb and better scores for 'usual activities' were observed with high dose i.v. iron compared with oral iron [42].

Similarly, compared with oral iron, the use of i.v. iron for treating post-partum anaemia has been shown to result in greater and faster Hb increase, better replenishment of iron stores, lower incidence of adverse side-effects and greater improvement in quality of life [15,46].

Therefore, should postoperative iron therapy be indicated, i.v. formulations are recommended. This is in line with recent management guidelines in surgical patients experiencing severe bleeding (GRADE 2C for i.v. iron preparations postoperatively) [7]. For calculating the total iron dose, it is important to take into account the preoperative haemoglobin level and iron status, the magnitude of postoperative haemoglobin drop, and whether patients have received postoperative red cell transfusion (Figure 1). The use of i.v. iron formulations which allow quick (15-60 mins) infusion of high iron doses

(1000 mg or more) offers added convenience to both physicians and patients and should be preferred, despite their higher cost (Table 1) [40,64].

Which are the true risks and contra-indications for intravenous iron?

Many clinicians and health authorities still consider that i.v. iron has a high association with major side effects, such as anaphylaxis, infections or oxidative stress. However, these side effects appear to be not significant with the newer i.v. iron preparations, such as ferric carboxymaltose, iron isomaltoside and low molecular weight iron dextran [64-66].

After an extensive data review, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that "*all i.v. iron medicines have a small risk of causing allergic reactions which can be life-threatening if not treated promptly*" [67]. However, the reported incidence of potentially life-threatening hypersensitivity reactions (<1:250.000 administrations) is vastly overestimated and the pathophysiological mechanism poorly understood, though a substantial proportion is thought to be mediated by complement activation, resulting complement activation-related pseudo allergy (CARPA)[68,69]. Minor infusion reactions due to 'labile' iron may occur, but are usually self-limiting without intervention and should not be misinterpreted as acute hypersensitivity events [65,70].

The CHMP's review also concludes that "*the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimise the risk of allergic reactions*" [67]. To this end, i.v. iron preparations should only be given in an environment where resuscitation facilities are available, so that patients who develop an allergic reaction can be treated immediately, and patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of intravenous iron medicine[1]. Guidelines for adequate diagnosis and management of these reactions have been recently published [71]. In addition, the CHMP's report contraindicates the use of i.v. in patients with

hypersensitivity to the active substance or excipients, with serious hypersensitivity to other parenteral iron products, or in the first trimester of pregnancy [67].

Elemental iron is an essential growth factor for bacteria, with many species expressing iron transport proteins that compete with transferrin, and it has long been suggested that patients with iron overload are at increased risk of infection [72]. However, data from meta-analyses and large observational studies showed that peri-operative i.v. iron did not increase postoperative infection or 30-day mortality rates in surgical patients [64,66]. In contrast, red cell transfusion delivers haem and labile iron which readily supports bacterial growth more [73]. Nevertheless, in the absence of definitive clinical data, it would seem logical to refrain from i.v. iron administration in an acute infection setting [8].

The available evidence relating i.v. iron administration to oxidative stress leading to atherogenesis and vascular remodelling is sparse and indirect. It is mostly derived from observational retrospective studies addressing long-term i.v. iron therapy [70], while in the postoperative period, very short-term i.v. iron courses are administered (one or two large doses) [64]. Thus, it does not seem to be a concern in the postoperative setting.

Should we treat iron deficiency without anaemia?

A normal haemoglobin level does not exclude iron deficiency. In fact, the WHO recognises that 'mild' anaemia (haemoglobin 110-130 $g.l^{-1}$) is a misnomer, as iron deficiency is already advanced by the time anaemia is detected, and has consequences even when anaemia is not clinically apparent [18].

Non-anaemic patients with reduced or absent iron stores may have symptoms such as fatigue or reduced exercise tolerance, as iron is required for optimal mitochondrial function essential for respiration and energy production [40,74]. Current guidelines do not recommend routine iron screening in the absence of anaemia. However, the benefit of oral or i.v. iron replacement for non-anaemic iron deficiency-associated

fatigue has been demonstrated in menstruating women, runners and blood donors [75-78].

In congestive heart failure, a frequent comorbidity among surgical patients, non-anaemic iron deficiency was independently associated with compromised physical performance and quality of life, and an increase of all-cause and cardiovascular mortality; treatment of non-anaemic iron deficiency with i.v. iron may improve functional status within four weeks, and reduces hospitalisations for cardiovascular reasons and mortality [79,80]. In addition, improvements are maintained after 24 and 52 weeks [79-81].

In observational studies of patients undergoing abdominal or cardiac surgery, pre-operative non-anaemic iron deficiency was associated with poor outcomes, including increased rates of postoperative infection, transfusion, fatigue and longer length of hospital stay [82-84]. Though it is presently unknown whether preoperative correction of non-anaemic iron deficiency may offset the excess of risk of postoperative complications, some guidelines recommend peri-operative iron supplementation for patients with non-anaemic iron deficiency [14,85].

Secondary thrombocytosis can be also seen after major surgery, as platelets behave as an acute phase reactant. Iron deficiency has also been shown to induce secondary thrombocytosis in several clinical settings. Correction of iron deficiency usually lowers platelet count and platelet activation in patients with chronic kidney disease, cancer or inflammatory bowel disease-associated secondary thrombocytosis, and might contribute to reduced risk of thrombo-embolic events [86-89].

Is there a role for erythropoiesis stimulating agents?

In patients without a previous indication, postoperative administration of recombinant erythropoietin [rHuEPO] is an *off-label* use of this medicinal product. The effects of postoperative rHuEPO have been evaluated in case series, mostly in Jehovah Witnesses, and in two RCTs yielding inconclusive results due to selection bias [58] or premature interruption [59].

In women with moderate-to-severe postpartum anaemia, 5 RCTs evaluated the effects of iron sucrose (300-1600 mg) or iron sucrose plus rHuEPO (20,000-40,000 IU) on haemoglobin recovery and transfusion needs [15]. A trend to faster Hb increment was observed with rHuEPO plus i.v iron compared with i.v. iron alone, but no significant differences in transfusion rate were observed, which were very low. The benefit seemed to be greatest in rHuEPO-treated subgroup with elevated C-reactive protein levels after Caesarean section [15].

Though it does not strictly refer to surgical patients, a recent meta-analysis also found a reduction of mortality rates (risk ratio [RR] 0.63, 95% CI 0.49–0.79, P < 0.0001) in critically ill trauma patients receiving rHuEPO (nine studies, 2607 patients), without increasing the risk of thromboembolic complications [90]. In cardiac surgery patients, rHuEPO seems to exert a neurologic and renal protective effect [91,92]. The mechanisms underlying these non-erythropoietic effects of rHuEPO need to be elucidated before recommending its use in patients without an approved indication.

Short-term pre-operative (1-4 days prior to operation) administration of rHuEPO to anaemic patients, with or without i.v. iron, has been shown to reduce postoperative transfusion in elective orthopaedic and cardiac surgery [93,94]. In hip fracture repair surgery there are conflicting results. One RCT failed to show a reduction in red cell transfusion in patients receiving rHuEPO plus i.v. iron [95]. However they included patients with haemoglobin <100 $g.l^{-1}$ and excluded women with haemoglobin ≥120 $g.l^{-1}$, and fixed amounts of red cell according pre-defined transfusion thresholds (e.g., patients with haemoglobin ≤70 $g.l^{-1}$ received 3 units of red cells and those with haemoglobin 71 to 89 $g.l^{-1}$ and severe symptoms received two units). In contrast, an observational study in 196 anaemic hip fracture patients managed with perioperative i.v. iron and restrictive transfusion protocol, administration of recombinant erythropoeitin on admission was associated with reduced transfusion requirements and higher haemoglobin levels on discharge and postoperative day 30 [98]. An analysis including 544 women with haemoglobin <130 $g.l^{-1}$ undergoing hip fracture repair showed that the blood sparing effect of this strategy was restricted to those presenting with haemoglobin concentrations between 120 and 130 $g.l^{-1}$ (n= 305)[97].

Thus, in non-cancer patients with severe postoperative anaemia and blunted erythropoiesis due to infection and/or inflammation, as well as in those who refuse blood transfusion, we suggest considering treatment with recombinant human erythropoietin. However, some guidelines do not support the off-label use of this medicinal product [12].

Red blood cell transfusion: transfusion thresholds for whom and when?

Allogeneic red cell transfusion is associated with a significant increase in peri-operative morbidity and mortality [2,98-100]. In addition, there is a worldwide shortage of blood with substantial associated costs to the manufacturer and health systems [101]. Moreover, red cell transfusion harbours the risk of infectious, immunological, haemolytic, non-haemolytic adverse reactions, cardiac and pulmonary complications [2,98]. Despite successful implementation of PBM programs, red cell transfusion is still widely used as a default treatment the majority of patients with acute postoperative anaemia [102].

Historically, the standard for red cell transfusion was a liberal transfusion threshold, namely haemoglobin level <100 $g.l^{-1}$ (or haematocrit <30%). This arbitrary transfusion threshold has been gradually lowered towards haemoglobin 70 – 80 $g.l^{-1}$, according to data derived from a number of randomised controlled trials (RCT) evaluating the effect on patients' outcomes of restrictive versus more liberal red cell transfusion strategies in a variety of clinical settings. When subjected to pooled analysis in several systematic reviews and meta-analyses (On-line appendix 2) [103-108], data from these RCTs show that, in terms of morbidity and mortality, a restrictive red cell transfusion strategy is equivalent to or more beneficial than a liberal strategy [101,109] .

In addition, evidence-based guidelines have translated the results of RCTs and meta-analyses into clinical practice [7,10-12,47-49]. One of the most recently published guidelines on red cell transfusion thresholds recommends a restrictive red cell transfusion threshold (haemoglobin <70 $g.l^{-1}$) for hospitalised adult patients who are haemodynamically stable, including critically ill patients [49]. However, a transfusion threshold of at least 80 $g.l^{-1}$ is suggested for patients undergoing orthopaedic surgery,

cardiac or oncological surgery, and those with pre-existing cardiovascular disease [12,49,110,111]. Nevertheless, transfusion of red cells for higher haemoglobin levels should be evaluated case by case considering acute on-going blood loss, comorbidities and signs of organ ischaemia or symptoms indicative of hypoxia, and compared with postoperative functional recovery and morbidity. In any case, published guidelines, agree that red cell transfusion is not beneficial when haemoglobin is >100 $g.l^{-1}$ [7,10-12,47-49,112]. Confounding factors on haemoglobin levels have to be considered, as discussed above.

Cost assessment implications

There are very few studies on the cost implications of the management of postoperative anaemia. Most such studies have evaluated pre-operative interventions, and since the pre-operative haemoglobin value is strongly associated with the postoperative haemoglobin, interventions aimed to improve pre-operative anaemia also influence postoperative well-being and its related costs [113].

Costs of anaemia management and PBM may vary from institution to institution and depend on the extent to which different aspects of PBM have been implemented. The following costs per patient were recently calculated in a single German University Hospital: diagnosis of anaemia €49-124; treatment of anaemia (including iron-deficiency anaemia and megaloblastic anaemia) €13-128 [114].

Similarly, data from > 600,000 patients (2008-2014) who were enrolled in a PBM, peri-operative management programme targeting anaemia and iron deficiency, a risk-adjusted reduction of postoperative red cell transfusion, infection and mortality rates, shorten length of hospital stay, and US$ 78-97 million estimated activity-based savings was reported [2].

A recent RCT that investigated the use of i.v. iron versus standard care in the management of postoperative anaemia did not include a formal cost-analysis; however, transfusion rate, infections and hospital stay were decreased, suggesting cost effectiveness [39]. A retrospective, matched cohort reported on costs of postoperative i.v. iron therapy in total lower limb arthroplasty and found that use of iron formulations was cost-neutral (-25.5 to 62.1 €/patient for iron sucrose and -51.1

to 64.4 €/patient for ferric carboxymaltose) compared with red cell transfusion [43]. In contrast, although NICE guidelines still recommend oral iron in the pre-operative and postoperative settings [12], available evidence on the lack of efficacy of oral iron in the postoperative period suggests that cost-analysis of this intervention is not meaningful [51-57].

Suggestions for further research

During the writing of this consensus statement, it became apparent that there are areas of postoperative anaemia management for which further research is required:

- **Monitoring.** It is really important to emphasise the need for detailed post-discharge anaemia studies with periodical monitoring of haemoglobin and iron parameters in relation to functional recovery.
- **Interventions.** More data and clinical trials are required to firmly establish the impact of postoperative anaemia management strategies (i.v. iron vs. oral iron, recombinant erythropoietin, red cell transfusion, and nutritional support) on functional recovery and quality of life, on end–points in addition to laboratory end-points, such as haemoglobin increase, and interventional end-points, such as reduction or avoidance of red cell transfusion. Further research is required to assess the effects of correction of iron deficiency, with or without anaemia, on platelet counts, platelet activation, and thromboembolic events, especially in the elderly. Timing of interventions in the postoperative course needs to be addressed in future trials. Dosing of anti-anaemia treatment and combination of means of treatment must be systematically investigated.
- **Patients.** It is also needed to define which patient groups are most likely to benefit from such treatments
- **Mechanisms of action.** The mechanisms underlying non-erythropoietic effects of recombinant erythropoietin, such as neurological and renal protective effects, and iron need to be elucidated.
- **Cost.** Cost-effectiveness of postoperative anaemia correction must be investigated at the different time points for its administration, and a formal cost evaluation. Until such data are available, the predominant signal from

available publications and peer reviewed recommendation support the concept of postoperative anaemia screening, diagnosis and appropriate treatment.

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References

1. SABM. Anemia prevention and management program implementation guide,2015 https://www.sabm.org/sites/default/files/anemia_prevention_management_program_implementation_guide.pdf (accessed 11/10/ 2017).
2. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. *Transfusion* 2017; **57**:1347-58.
3. Muñoz M, Gómez-Ramírez S, Kozek-Langeneker S, et al. 'Fit to fly': overcoming barriers to preoperative haemoglobin optimization in surgical patients. *British Journal of Anaesthesia* 2015; **115**:15-24.
4. Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017; 72:233-47.
5. Meybohm P, Richards T, Isbister J, et al. Patient Blood Management Bundles to Facilitate Implementation. *Transfusion Medicine Reviews* 2017; **31**:62-71.
6. Spahn DR. Patient Blood Management: the new standard. *Transfusion* 2017; **57**:1325-7.
7. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. First update 2016. *European Journal of Anaesthesiology* 2017; **43**: 332-95.
8. Beris P, Muñoz M, García-Erce JA, Thomas D, Maniatis A, Vander Linden P. Perioperative anaemia management: consensus statement on the role of intravenous iron. *British Journal of Anaesthesia* 2008; **100**: 599–604.
9. National Blood Authority. Patient Blood Management Guidelines: Module 2 - Perioperative. https://www.blood.gov.au/pbm-module-2 (accessed 11/10/2017).
10. Leal-Noval SR, Muñoz M, Asuero M, et al; Spanish Expert Panel on Alternatives to Allogeneic Blood Transfusion. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document". *Blood Transfusion 2013*; **11**:585-610.
11. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* 2015; **122**:241-75.

12. NICE guideline [NG24]. Blood transfusion. https://www.nice.org.uk/guidance/ng24/chapter/Recommendations#alternatives-to-blood-transfusion-for-patients-having-surgery-2 (accessed 27/06/ 2017)
13. Vaglio S, Prisco D, Biancofiore G, et al. Recommendations for the implementation of a Patient Blood Management programme. Application to elective major orthopaedic surgery in adults. *Blood Transfusion* 2016; **14**: 23-65.
14. Kotzé A, Harris A, Baker C, et al. British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia. *British Journal of Haematology* 2015; **171**:322-31.
15. Muñoz M, Peña-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfusion Medicine 2017 [Jul 19. doi: 10.1111/tme.12443].
16. Shander A, Knight K, Thurer R, Adamson J, Spence R. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. *American Journal of Medicine* 2004; **116**:58S-69S.
17. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. *Anesthesiology* 2010; **113**:482-95.
18. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. WHO/NMH/NHD/MNM/11.1. http://www.who.int/vmnis/indicators/haemoglobin.pdf (accessed 28/04/2017).
19. Butcher A, Richards T, Stanworth S J, Klein, A. A. Diagnostic criteria for pre-operative anaemia–time to end sex discrimination. *Anaesthesia* 2017; **72**: 811–814.
20. Muñoz M, Shander A, Rijhwani T, Dyga R, Waters JH. Postoperative blood management strategies. In: Frank SM, Waters JH (eds) Patient Blood Management: Multidisciplinary approaches to optimizing care. Bethesda: AABB Press, 2016: 233-58.
21 Hayn D, Kreiner K, Kastner P, et al. Data Driven Methods for Predicting Blood Transfusion Needs in Elective Surgery. *Studies in Health Technology and Informatics* 2016; **223**:9-16.
22. Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. *Current Opinion in Hematology* 2005; **12**:123-8
23. Gómez-Ramírez S, Remacha-Sevilla ÁF, Muñoz-Gómez M. Anaemia in the elderly. *Medicina Clinica (Barcelona)* 2017; **149**: 496-503.

24. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. *Critical Care Medicine* 2000; **28**:2773-8.

25. van Iperen CE, Kraaijenhagen RJ, Biesma DH, Beguin Y, Marx JJ, van de Wiel A. Iron metabolism and erythropoiesis after surgery. *British Journal of Surgery* 1998; **85**:41-5.

26. Muñoz M, García-Erce JA, Remacha AF. Disorders of iron metabolism. Part II: Iron deficiency and iron overload. *Journal of Clinical Pathology* 2011; **64**: 287-296.

27. Goodnough LT, Maggio P, Hadhazy E, et al. Restrictive blood transfusion practices are associated with improved patient outcomes. *Transfusion* 2014; **54**:2753-9.

28. So-Osman C1, Nelissen R, Brand R, Brand A, Stiggelbout AM. Postoperative anemia after joint replacement surgery is not related to quality of life during the first two weeks postoperatively. *Transfusion* 2011;**51**:71-81.

29. Vuille-Lessard E, Boudreault D, Girard F, Ruel M, Chagnon M, Hardy JF. Postoperative anemia does not impede functional outcome and quality of life early after hip and knee arthroplasties. *Transfusion* 2012; **52**:261-70.

30. Jans O, Bandholm T, Kurbegovic S, et al. Postoperative anemia and early functional outcomes after fast-track hip arthroplasty: a prospective cohort study. *Transfusion* 2016; **56**:917-25.

31. Koch CG, Li L, Sun Z, et al. Magnitude of anemia at discharge increases 30-day hospital readmissions. *Journal of Patient Safety* 2017;**13**:202-6.

32. Choi YJ, Kim SO, Sim JH, Hahm KD. Postoperative anemia is associated with acute kidney injury in patients undergoing total hip replacement arthroplasty: A retrospective study. *Anesthesia & Analgesia* 2016;**122**:1923-8.

33. Pitter FT, Jorgensen CC, Lindberg-Larsen M, Kehlet H. Postoperative morbidity and discharge destinations after fast-track hip and knee arthroplasty in patients older than 85 years. *Anesthesia & Analgesia* 2016; **122**:1807-15.

34. Jorgensen CC, Kehlet H. Early thromboembolic events </=1week after fast-track total hip and knee arthroplasty. *Thrombosis Research* 2016; **138**:37-42.

35. Gayat E, Aulagnier J, Matthieu E, Boisson M, Fischler M. Non-invasive measurement of hemoglobin: assessment of two different point-of-care technologies. *PLoS One* 2012; **7**:e30065.

36. Barker SJ, Shander A, Ramsay MA. Continuous Noninvasive Hemoglobin Monitoring: A Measured Response to a Critical Review. *Anesthesia & Analgesia* 2016; **122**:565-72.

37. Noumi B1, Teruya S, Salomon S, Helmke S, Maurer MS. Blood volume measurements in patients with heart failure and a preserved ejection fraction: implications for diagnosing anemia. Congestive Heart Failure 2011; **17**:14-8.

38. Muñoz M, García-Erce JA, Remacha AF. Disorders of iron metabolism. Part 1: molecular basis of iron homoeostasis. *Journal of Clinical Pathology* 2011; **64**:281-6.

39. Khalafallah AA, Yan C, Al-Badri R, et al. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial. *Lancet Haematology* 2016; **3**:e415-25.

40. Cappellini MD, Comin-Colet J, de Francisco A, et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis and management. *American Journal of Hematology* 2017; **92**:1068-78.

41. Thomas L, Thomas C. Detection of iron restriction in anaemic and non-anaemic patients: New diagnostic approaches. *European Journal of Haematology* 2017; **99**: 262-8.

42. Bisbe E, Moltó L, Arroyo R, Muniesa JM, Tejero M. Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. *British Journal of Anaesthesi*a 2014; **113**:402-9.

43. Muñoz M, Gómez-Ramírez S, Martín-Montañez E, Naveira E, Seara J, Pavía J. Cost of post-operative intravenous iron therapy in total lower limb arthroplasty: a retrospective, matched cohort study. *Blood Transfusion* 2014; **12**:40-9.

44. Johansson PI, Rasmussen AS, Thomsen LL. Intravenous iron isomaltoside 1000 (Monofer®) reduces postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination thereof: a randomized double-blind placebo-controlled clinical trial (the PROTECT trial). *Vox Sanguinis* 2015; **109**:257-66.

45. Kim Yw, Bae JM, Park YK, et al and study group. Effect of Intravenous Ferric Carboxymaltose on Hemoglobin Response Among Patients With Acute Isovolemic AnemiaFollowing Gastrectomy: The FAIRY Randomized Clinical Trial. JAMA 2017; 317:2097-104.

46. Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. *Vox Sanguinis* 2017; **112**:219-28.

47. Liumbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossetti G; Italian Society of Transfusion Medicine and Immunohaematology Working Party. Recommendations for

the transfusion management of patients in the peri-operative period. III. The post-operative period. *Blood Transfusion* 2011; **9**:320-35.

48. Klein AA, Arnold P, Bingham RM, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. *Anaesthesia* 2016; **71**:829-42.
49. Carson JL, Guyatt G, Heddle NM, et al. Red Blood Cell Transfusion: 2016 Clinical Practice Guideline from the AABB. *Annals of Internal Medicine* 2016; **316**:2025-35.
50. Vaglio S, Gentili S, Marano G, et al. The Italian Regulatory Guidelines for the implementation of Patient Blood Management. *Blood Transfusion* 2017; **15**:325-8.
51. Crosby L, Palarski VA, Cottington E, Cmolik B. Iron supplementation for acute blood loss anemia after coronary artery bypass surgery: a randomized, placebo-controlled study. *Heart & Lung* 1994; **23**:493-9.
52. Sutton PM, Cresswell T, Livesey JP, Speed K, Bagga T. Treatment of anaemia after joint replacement. A double-blind, randomised, controlled trial of ferrous sulphate versus placebo. *Journal of Bone and Joint Surgery Britain* 2004; **86**:31-3.
53. Weatherall M, Maling TJ. Oral iron therapy for anaemia after orthopaedic surgery: randomized clinical trial. *ANZ Journal of Surgery* 2004; **74**:1049-51.
54. Mundy GM, Birtwistle SJ, Power RA. The effect of iron supplementation on the level of haemoglobin after lower limb arthroplasty. *Journal of Bone and Joint Surgery Britain* 2005;**87**:213-7.
55. Zauber NP, Zauber AG, Gordon FJ, et al. Iron supplementation after femoral head replacement for patients with normal iron stores. *JAMA* 1992; **267**:525-7.
56. Prasad N, Rajamani V, Hullin D, Murray JM. Post-operative anaemia in femoral neck fracture patients: does it need treatment? A single blinded prospective randomised controlled trial. *Injury* 2009;**40**:1073-6.
57. Parker MJ. Iron supplementation for anemia after hip fracture surgery: a randomized trial of 300 patients. *Journal of Bone and Joint Surgery America* 2010; **92**:265-9.
58. Madi-Jebara SN, Sleilaty GS, Achouh PE, et al. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. *Journal of Cardiothoracic Vascular Anesthesia* 2004;**18**:59-63.
59. Karkouti K, McCluskey SA, Ghannam M, Salpeter MJ, Quirt I, Yau TM. Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia. *Canadian Journal of Anaesthesia* 2006; **53**:11-9.
60. Mudge DW, Tan KS, Miles R, et al. A randomized controlled trial of intravenous or oral iron for posttransplant anemia in kidney transplantation. *Transplantation* 2012; **93**:822-6.

61. Titos-Arcos JC, Soria-Aledo V, Carrillo-Alcaraz A, Ventura-López M, Palacios-Muñoz S, Pellicer-Franco E. Is intravenous iron useful for reducing transfusions in surgically treated colorectal cancer patients? *World Journal of Surgery* 2012; **36**:1893-7.

62. Garrido-Martín P, Nassar-Mansur MI, de la Llana-Ducrós R, et al. The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: a randomized clinical trial. *Interactive Cardiovascular Thoracic Surgery* 2012; **15**:1013-8.

63. Jeong O, Park YK. Effect of intravenous iron supplementation for acute postoperative anemia in patients undergoing gastrectomy for gastric carcinoma: a pilot study. *Annals of Surgical Oncology* 2014; **21**:547-52.

64. Muñoz M, Gómez-Ramírez S, Besser M, et al. Current misconceptions in diagnosis and management of iron deficiency. *Blood Transfusion* 2017; **15**:422-37.

65. Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. *Lance*t 2007; **369**: 1502-4.

66. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clinic Proceedings* 2015; **90**:12-23.

67. European Medicines Agency. New recommendations to manage risk of allergic reactions with intravenous iron containing medicines. EMA/579491/2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500151308.pdf (accessed: 18 June 2017).

68. Auerbach M, Adamson J, Bircher A, et al. On the safety of intravenous iron, evidence trumps conjecture. *Haematologica* 2015; **100**:e214-5

69. Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. *British Journal of Pharmacology* 2015; **172**:5025-36.

70. Macdougall IC, Bircher AJ, Eckardt KU, et al; Conference Participants. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney International* 2016; **89**:28-39.

71. Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014; **99**:1671-6.

72. Ganz T. Iron in innate immunity: starve the invaders. *Current Opinion in Immunology* 2009; **21**:63-7.

73. Andrews SC, Robinson AK, Rodríguez-Quiñones F. Bacterial iron homeostasis. *FEMS Microbiology Reviews* 2003; **27**:215–37.

74. Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: a systematic review. *European Journal of Haematology* 2016; **96**:618-28.

75. Sharma R, Stanek JR, Koch TL, et al. Intravenous iron therapy in non-anemic iron-deficient menstruating adolescent females with fatigue. Am J Hematol 2016; 91:973-7.

76. Burden RJ, Morton K, Richards T, et al. Is iron treatment beneficial in, iron-deficient but non-anaemic (IDNA) endurance athletes? A systematic review and meta-analysis. *British Journal of Sports Medicine* 2015; **49**:1389.

77. Pittori C, Buser A, Gasser UE, et al. A pilot iron substitution programme in female blood donors with iron deficiency without anaemia. *Vox Sanguinis* 2011; **100**:303-11.

78. Krayenbuehl PA, Battegay E, Breymann C, Furrer J, Schulthess G. Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. *Blood* 2011; **118**:3222-7.

79. Anker SD, Comin Colet J, Filippatos G, et al; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *New England Journal of Medicine* 2009; **361**:2436-48.

80. Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *European Journal of Heart Failure* 2016; **18**:786-95.

81. Goodnough LT, Comin-Colet J, Leal-Noval S, et al. Management of anemia in patients with congestive heart failure. *American Journal of Hematology* 2017; **92**:88-93.

82. Harju E. Empty iron stores as a significant risk factor in abdominal surgery. *Journal of Parenteral and Enteral Nutrition* 1988; **12**: 282-5.

83. Piednoir P, Allou N, Driss F, et al. Preoperative iron deficiency increases transfusion requirements and fatigue in cardiac surgery patients: a prospective observational study. *European Journal of Anaesthesiology* 2011; **28**:796-801.

84. Miles LF, Kunz SA, Na LH, Braat S, Burbury K, Story DA. Postoperative outcomes following cardiac surgery in non-anaemic iron-replete and iron-deficient patients - an exploratory study. *Anaesthesia* 2017 (doi: 10.1111/anae.14115. Epub ahead of print).

85. Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *British Journal of Anaesthesia* 2011; **106**:13-22.

86. Kulnigg-Dabsch S, Schmid W, Howaldt S, et al. Iron deficiency generates secondary thrombocytosis and platelet activation in IBD: the randomized, controlled thromboVIT trial. *Inflammatory Bowel Diseases* 2013; **19**:1609-16.

87. Henry DH, Dahl NV, Auerbach MA. Thrombocytosis and venous thromboembolism in cancer patients with chemotherapy induced anemia may be related to ESA induced iron restricted erythropoiesis and reversed by administration of IV iron. *American Journal of Hematology* 2012; **87**:308-10

88. Hazara AM, Bhandari S. Intravenous iron infusion reduces platelet counts in patients with chronic kidney disease. *Journal of Clinical Pharmacology Therapeutic* 2015; **40**: 20-23.

89. Kaiafa G, Savopoulos C, Kanellos I, et al. Anemia and stroke: Where do we stand? *Acta Neurologica Scandinavica* 2017; **135**:596-602.

90. French CJ, Glassford NJ, Gantner D, et al. Erythropoiesis-stimulating Agents in Critically Ill Trauma Patients: A Systematic Review and Meta-analysis. *Annals of Surgery* 2017; **265**:54-62.

91. Penny-Dimri JC, Cochrane AD, Perry LA, Smith JA. Characterising the role of perioperative erythropoietin for preventing acute kidney injury after cardiac surgery: systematic review and meta-analysis. *Heart Lung Circulation* 2016; **25**:1067-76.

92. Lakič N, Mrak M, Šušteršič M, Rakovec P, Bunc M. Perioperative erythropoietin protects the CNS against ischemic lesions in patients after open heart surgery. *Wiener Klinische Wochenschrift* 2016; **128**:875-81.

93. Weltert L, Rondinelli B, Bello R, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. *Transfusion* 2015; **55**:1644-54.

94. Cuenca J, García-Erce JA, Martínez F, Pérez-Serrano L, Herrera A, Muñoz M. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. *Transfusion* 2006; **46**:1112-9

95. Bernabeu-Wittel M, Romero M, Ollero-Baturone M, et al; PAHFRAC-01 Investigators. Ferric carboxymaltose with or without erythropoietin in anemic patients with hip fracture: a randomized clinical trial. *Transfusion* 2016; **56**:2199-211

96. García-Erce JA, Cuenca J, Haman-Alcober S, Martínez AA, Herrera A, Muñoz M. Efficacy of preoperative recombinant human erythropoietin administration for reducing transfusion requirements in patients undergoing surgery for hip fracture repair. An observational cohort study. *Vox Sanguinis* 2009; **97**:260-7.

97. Muñoz M, Gómez-Ramírez S, Auerbach M. Stimulating erythropoiesis before hip fracture repair for reducing blood transfusion: should we change the hemoglobin cutoff level for defining anemia in females? *Transfusion* 2016; **56**:2160-3.

98. Meybohm P, Herrmann E, Steinbicker AU; PBM-study Collaborators. Patient Blood Management is associated with a substantial reduction of red blood cell utilization and safe for patient's outcome: a prospective, multicenter cohort study with a non-inferiority design. *Annals of Surgery* 2016; **264**:203-11.

99. Goodnough LT, Shieh L, Hadhazy E, et al. Improved blood utilization using real-time clinical decision support. *Transfusion* 2014; **54**:1358–65.

100. Gross I, Seifert B, Hofmann A, et al. Patient blood management in cardiac surgery results in fewer transfusions and better outcome. *Transfusion* 2015; **55**:1075–81.

101. Franchini M, Marano G, Mengoli C, et al. Red blood cell transfusion policy: a critical literature review. *Blood Transfusion* 2017; **15**:307-17.

102. Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. *Transfusion Medicine Reviews* 2011; **25**:89-101.

103. Curley GF, Shehata N, Mazer CD, Hare GM, Friedrich JO. Transfusion thresholds for guiding RBC transfusion for cardiovascular surgery: a systematic review and meta-analysis. *Critical Care Medicine* 2014; **42:** 2611-24.

104. Salpeter SR, Buckley JS, Chatterjee S. Impact of more restrictive blood transfusion strategies on clinical outcomes: a metaanalysis and systematic review. *American Journal of Medicine* 2014; **127:** 124-31.

105. Brunskill SJ, Millette SL, Shokoohi A, et al. Red blood cell transfusion for people undergoing hip fracture surgery. *Cochrane Database Systematic Reviews* 2015; **4:** CD009699.

106. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *British Medical Journal* 2015; **350:** h1354.

107. Ripollés Melchor J, Casans Francés R, Espinosa A, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion in critically ill patients and in patients with acute coronary syndrome: s systematic review, meta-analysis and trial sequential analysis. *Minerva Anestesiologica* 2016; **82:** 582-98.

108. Carson JL, Stanworth SJ, Roubinian NR, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Systematic Reviews* 2016; **10:** CD002042.
109. Liumbruno GM, Vaglio S, Biancofiore G, et al. Transfusion thresholds and beyond. *Blood Transfusion* 2016; **14**:123-5.
110. de Almeida JP, Vincent JL, Galas FR, et al. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. *Anesthesiology* 2015; **122**:29-38.
111. Bergamin FS, Almeida JP, Landoni G, et al. Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. *Critical Care Medicine* 2017; **45**:766-73.
112. Shander A, Gross I, Hill S, Javidroozi M, Sledge S. A new perspective on best transfusion practices. *Blood Transfusion* 2013; **11**: 193-202.
113. Muñoz M, Gómez-Ramírez S, Kozek-Langeneker S. Pre-operative haematological assessment in patients scheduled for major surgery. *Anaesthesia* 2016; **71** (Suppl 1):19-28.
114. Kleinerüschkamp AG, Zacharowski K, Ettwein C, et al [Cost analysis of patient blood management]. *Anaesthesist* 2016; **65**:438-48.

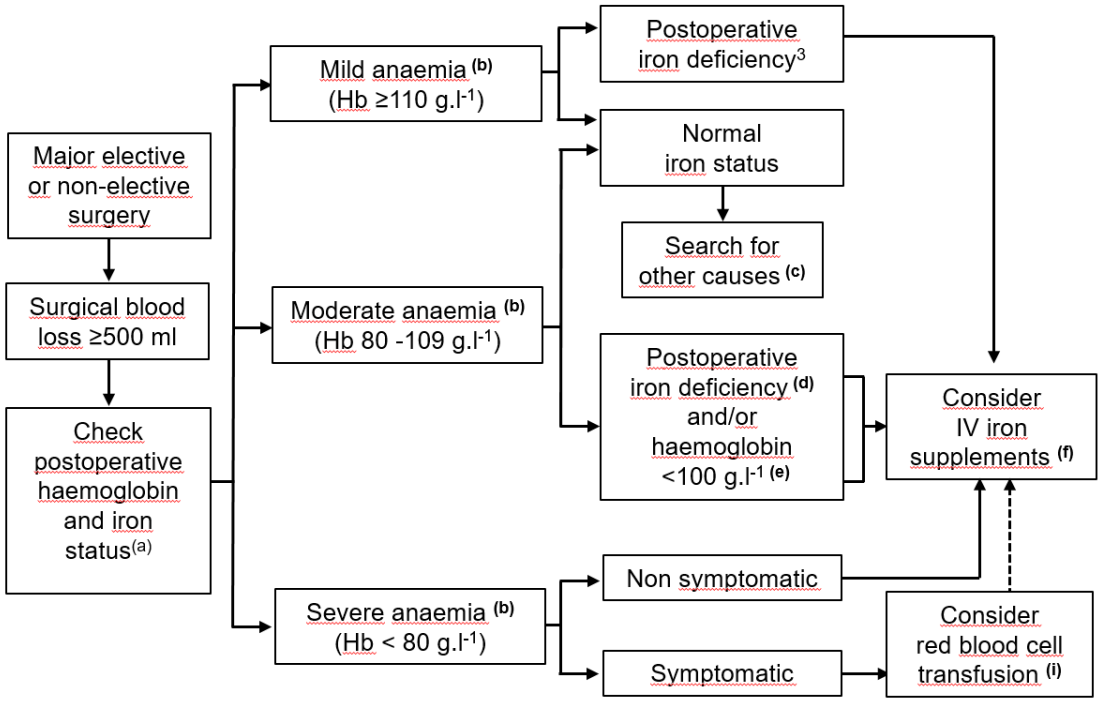
Legend to figures

Figure 1. Postoperative anaemia management

a. Whenever possible, assess iron status within 24h postop, if it has not been already performed in the pre-operative assessment. Monitor haemoglobin during 3-4d postop.
b. According to World Health Organisation's classification.
c. Appropriate treatment should be considered.
d. Postoperative ferritin <100 $\mu g.l^{-1}$, ferritin <300 $\mu g.l^{-1}$ and transferrin saturation <20% or reticulocyte haemoglobin content <28 pg.
e. Due to preoperative anaemia or heavy surgical bleeding.
f. Total iron deficiency = (target haemoglobin – actual haemoglobin) x weight (kg) x 0.24.
    - Add another 10 $mg.kg^{-1}$ for replenishing iron stores, specially in patients with preop iron deficiency.
    - Consider adding recombinant human erythropoietin (40,000 IU) for patients with severe anaemia or declining transfusion.
    - For IV iron dosing schedule, see table 1.

i. Transfuse one red blood cell unit at the time, with post-transfusion reassessment of further needs. Consider IV iron supplementation after transfusion, using post-transfusion haemoglobin as actual haemoglobin for total iron deficiency calculation.

Figure 1


Major elective or non-elective surgery
Surgical blood loss ≥500 ml
Check postoperative haemoglobin and iron status(a)
Mild anaemia (b) (Hb ≥110 g.l-1)
Moderate anaemia (b) (Hb 80 -109 g.l-1)
Severe anaemia (b) (Hb < 80 g.l-1)
Postoperative iron deficiency3
Normal iron status
Search for other causes (c)
Postoperative iron deficiency (d) and/or haemoglobin <100 g.l-1 (e)
Non symptomatic
Symptomatic
Consider IV iron supplements (f)
Consider red blood cell transfusion (i)